

OPHTHALMICALLY-ACCEPTABLE AQUEOUS LIQUID COMPOSITION
COMPRISING A MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONIST

FIELD OF THE INVENTION

[001] The field of the invention relates to a heat-stable, ophthalmically-acceptable liquid composition comprising an amine buffer and a muscarinic acetylcholine receptor antagonist. The liquid composition may be stored in a heat-sterilized container. Methods of manufacturing such containers are also described.

BACKGROUND

[002] Pharmaceutical agents containing hydrolysable bonds can be unstable in aqueous liquid formulations, particularly when exposed to heat, resulting in decomposition to inactive, or toxic by-products. Liquid formulations containing such unstable agents can have a short shelf-life and thus often need to be made up at the point of care, or when prescribed, from a lyophilized powder. Alternatively, the formulations need to be filter-sterilized, which can cause processing problems.

[003] Atropine is a myopia management agent which safely and effectively slows down myopia progression. Under heated conditions or during long term storage, atropine degrades and produces by-products. In aqueous solutions, the major byproducts are dehydration product apoatropine and hydrolysis products of tropic acid and tropine. Among the degradation byproducts, apoatropine is about 20 times more toxic than atropine, which may raise the risk of drug safety or lead to reduced atropine dosage. There is a need to improve atropine's stability in aqueous solutions, minimizing toxicity with less dehydration products and increasing efficacy of atropine.

[004] Atropine is most stable around pH 4.0. The administration of eye drops at this acidic pH is uncomfortable for patients. There is a need for a stable atropine composition with a higher pH, which would be more acceptable to patients.

[005] Pirenzepine is another antimuscarinic agent and is commonly used to treat duodenal ulcers. It is also effective for controlling myopia progression in children. Although more stable than atropine, pirenzepine is still subject to significant hydrolysis, especially upon exposure to heat.

[006] Liquid pharmaceutical formulations typically contain a phosphate-based buffer, such as phosphate buffered saline. In the present invention, amine buffers are used as these have been found to reduce the hydrolysis of muscarinic acetylcholine receptor antagonists in aqueous formulations.

SUMMARY

[007] The present invention provides an ophthalmically-acceptable liquid composition comprising a muscarinic acetylcholine receptor antagonist, wherein the composition is heat-stable.

[008] The present invention also provides a heat-sterilized container containing a heat-stable ophthalmically-acceptable liquid composition of the invention.

[009] The present invention also provides a method of manufacturing a heat-sterilized container of the invention comprising: (a) placing an ophthalmically-acceptable packaging solution in a container, (b) sealing the container, and (c) heat sterilizing the sealed container, wherein the packaging solution is a liquid ophthalmically-acceptable formulation of the invention.

[010] Additional features and advantages of the present invention will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of the present invention. The objectives and other advantages of the present invention will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

[011] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide a further explanation of the present invention, as claimed.

[012] Unless stated otherwise, all % are weight% and are based on the total weight of the composition or solution.

[013] The accompanying drawing is incorporated in and constitute a part of this application and illustrate some of the features of the present invention. The drawing, together with the description, serve to explain the principles of the present invention.

BRIEF DESCRIPTION OF THE DRAWING

[014] **FIG. 1** shows the comparison of decomposition of atropine in citrate, phosphate and amine-based buffers over a pH range after autoclave sterilization.

DETAILED DESCRIPTION

[015] The present invention provides an ophthalmically-acceptable liquid composition comprising a muscarinic acetylcholine receptor antagonist, which is stable when subjected to heat such as through heat sterilization. The heat-stable ophthalmically-acceptable liquid composition comprises an amine buffer and a muscarinic acetylcholine receptor antagonist, wherein the muscarinic acetylcholine receptor antagonist comprises a hydrolysable bond.

[016] Typically, the liquid composition has a pH within the range of 5.0-7.5. Preferably the composition has a pH of 6.2 to 7.4, more preferably 6.3 to 7.2, more preferably 6.5 to 7.0, even more preferably 6.8 to 7.0. The pH is determined using a calibrated bench-top pH meter such as the Hanna HI 9321 benchtop pH meter or equivalent.

[017] The liquid composition is an aqueous composition which comprises an amine buffer which has an effective pH within the range 5.0-7.5. As used herein, an “amine buffer” comprises a buffering agent which contains an amine group. In one example, the amine group-containing buffering agent is the only buffering agent included in the composition. The amine group can be a primary, secondary or tertiary amine group.

[018] Suitable amine buffers or amine group-containing buffering agents include Tris(hydroxymethyl)aminomethane (Tris), N-(2-acetamido)iminodiacetic acid (ADA), bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane (Bis-Tris), 2-morpholinoethanesulfonic acid (MES), histidine, ethanolamine, hydrazine, imidazole, pyridine and piperazine. Preferably, the amine group-containing buffering agent is selected from Tris and Bis-Tris.

[019] The buffer agent may be present in the composition at any concentration sufficient to maintain an ophthalmically-acceptable pH (e.g., 5.8 to 7.4). Typically, the buffer agent is present at a molar concentration of 0.001M-0.5M. Preferably, the buffer agent is present at a molar concentration of 0.005M-0.2M, more preferably 0.006M-0.15 M, most preferably 0.008-0.12M.

[020] The presence of the amine buffer increases the heat-stability of the muscarinic acetylcholine receptor antagonist so that decomposition of the muscarinic acetylcholine receptor antagonist during heat sterilization is reduced as compared to a buffered composition lacking an amine group-containing buffering agent, such as phosphate buffered saline. In addition, the amine buffer may increase the shelf life, as the buffering agent prevents or reduces hydrolysis and/or degradation of the muscarinic acetylcholine receptor antagonist during storage. In some examples, the liquid composition remains stable when stored at room temperature (around 20°C) removing the need to refrigerate the liquid composition prior to or after first use. A liquid composition at ambient temperature is typically more comfortable to a patient when administered to the eye.

[021] As used herein, a “heat-stable” composition is one in which less than 10% (by weight) of the muscarinic acetylcholine receptor antagonist degrades during autoclave at 121°C (at 1 atm) for 30 minutes at 17 psi (hereinafter, “autoclave”). Thus, a heat-stable liquid composition of the invention can be packaged in a container and autoclaved to provide a heat-sterilized container wherein the amount of muscarinic acetylcholine receptor antagonist in the liquid composition following autoclave is no less than 90% (by weight) of an initial amount of the muscarinic acetylcholine receptor antagonist present in the liquid composition prior to heat-sterilization. In some examples, the amount of muscarinic acetylcholine receptor antagonist in the liquid composition is no less than 95% of an initial amount of the muscarinic acetylcholine receptor antagonist present in the composition prior to heat-sterilization. In some examples, the liquid composition that has been packaged in a container and autoclaved comprises less than 10% hydrolysed degradation products of the muscarinic acetylcholine receptor antagonist, and preferably less than 5% hydrolysed degradation products of the muscarinic acetylcholine receptor antagonist.

[022] Preferably, the autoclaved composition comprises at least 50% (by weight) fewer muscarinic acetylcholine receptor antagonist degradation products than an autoclaved control composition. As used herein, a “control composition” is a composition comprising phosphate buffered saline (PBS) having the formulation provided in Table 1 below instead of the amine buffer but is otherwise identical. In other words, a control composition has the same pH and amounts of muscarinic acetylcholine receptor antagonist and excipients as the amine buffer-containing composition to which it is being compared. Thus, for example, if a liquid composition comprising an amine buffer and 1.00 wt.% atropine is autoclaved and 0.95 wt.% atropine remains in the composition after autoclave, the autoclaved composition comprises 0.05 wt.% atropine

degradation products. If a control composition (i.e., comprising 1.00 wt.% atropine in PBS buffer) contains 0.80 wt.% atropine after autoclave, the autoclaved composition comprising the amine buffer has 75% fewer degradation products than the control composition. The heat-stable composition may comprise at least 60%, 75%, or 80% (by weight) fewer muscarinic acetylcholine receptor antagonist degradation products after autoclave than the control composition. The amount of degradation of a muscarinic acetylcholine receptor antagonist after autoclave can be determined by routine HPLC analysis, such as described in the examples below.

[023] While the compositions described herein are heat-stable, they may be sterilized using any known manner of sterilization, including by filtration methods typically used for ophthalmic formulations. In one example the composition is filtered through a 0.22 μm filter. The filter-sterilized, heat-stable composition may be stored and administered at room temperature, which can be more comfortable to the patient compared to the administration of ophthalmic formulations that require refrigeration.

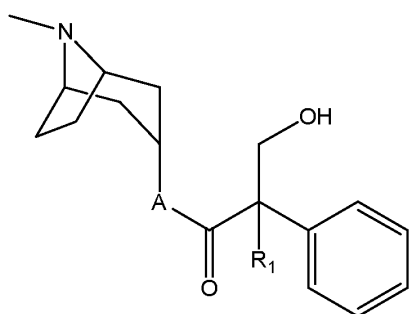
[024] The muscarinic acetylcholine receptor antagonist may be heat-sensitive. As used herein a “heat-sensitive muscarinic acetylcholine receptor antagonist” is a pharmaceutically active muscarinic acetylcholine receptor antagonist which is prone to degradation upon autoclave. In particular, less than 95% (by weight) of the initial amount of a heat-sensitive muscarinic acetylcholine receptor antagonist is present after autoclave when prepared as a 0.1% solution in PBS at pH 7.0. In some examples, less than 90% (by weight), or less than 80% (by weight), or less than 70% (by weight) of the initial amount of the heat-sensitive muscarinic acetylcholine receptor antagonist is present after autoclave.

[025] The muscarinic acetylcholine receptor antagonist comprises a hydrolysable bond. A hydrolysable bond is one which breaks through the process of hydrolysis. As used herein, a

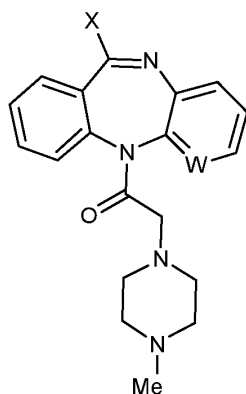
muscarinic acetylcholine receptor antagonist is considered to contain a hydrolysable bond if an aqueous solution of the muscarinic acetylcholine receptor antagonist contains at least 5% (by weight) breakdown products after autoclave. The hydrolysable bond may be an ester bond or an amide bond. In some examples, the hydrolysable bond is an ester bond or amide bond linked via one or more covalent bonds to an N-containing heterocyclic group. Examples of N-containing heterocyclic groups include substituted or unsubstituted aziridine, azirine, azetidine, azete, pyrrolidone, pyrrole, pyrimidine groups, imidazoline, pyrazolidine, imidazole, pyrazole, pyridine, piperidine, tetrazole, pentazole, diazine, diazinane, triazinane, triazine, tetrazine and tropane groups.

[026] The composition comprises a muscarinic acetylcholine receptor antagonist. Suitable muscarinic acetylcholine receptor antagonists include atropine, pirenzepine, scopolamine, trospium chloride, dicycloverine, oxybutynin, ipratropium bromide, and telenzepine. Preferably the muscarinic acetylcholine receptor antagonist is atropine or pirenzepine or a derivative or analog thereof, and pharmaceutically acceptable salts thereof. As used herein “atropine” includes D-atropine, L-atropine (hyoscyamine) or a racemic mixture, or a pharmaceutically acceptable salt thereof. Suitable salts include hydrochloride, sulfate, acetate, phosphate, diphosphate, chloride, maleate, citrate, mesylate, nitrate, tartrate, maleate, bicarbonate fumarate, tosylate, succinate, stearate and gluconate. Preferably the muscarinic acetylcholine receptor antagonist is atropine sulfate.

[027] In some examples, the composition comprises a muscarinic acetylcholine receptor antagonist of formula (I) or (II)



Formula (I)



Formula (II)

[028] in which A is O or NH;

[029] R₁ is H, D (deuterium), hydroxyl, alkoxy, nitrile, a halogen atom, a C₁-C₁₀ straight, branched or cycloalkyl group optionally substituted with one or more halogen atom; or a phenyl or benzyl group optionally substituted with one or more substituents selected from C₁-C₁₀ straight, branched or cycloalkyl group, haloalkyl group, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and each being optionally substituted with one or more substituents selected from C₁-C₁₀ straight, branched or cycloalkyl group, haloalkyl group, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms;

[030] X is -OH, O or -ONO₂,

[031] Me is CH₃; and

[032] W is N or CH.

[033] Preferably A is O.

[034] Preferably R₁ is H, D or a halogen atom. Preferably the halogen atom is F.

[035] Preferably A is O and R₁ is H, D or a halogen atom. Preferably the halogen atom is F.

[036] Preferably A is O and R₁ is H.

[037] Preferably X is O.

[038] Preferably W is N.

[039] Preferably X is O and W is N.

[040] The composition may comprise 0.001 wt.% to 5.0 wt.% muscarinic acetylcholine receptor antagonist. In some examples, the composition comprises 0.005 wt.% to 3.0 wt.%, or 0.01 wt.% to 2.0 wt.% muscarinic acetylcholine receptor antagonist.

[041] The composition is ophthalmically-acceptable which refers to a composition which may be in direct contact with the ocular environment without causing any physiological or pharmacological harmful effects. Initial stinging or minor discomfort is common with topical ophthalmic formulations and is not considered harmful. The compositions disclosed herein have the advantage of reducing or eliminating the stinging or discomfort associated with previous ophthalmic formulations of muscarinic acetylcholine receptor antagonists.

[042] The use of heat sterilization, as opposed to filter sterilization removes the need for a preservative. Preferably the composition does not contain a preservative, so the composition is preservative-free. In some examples the composition comprises less than 0.001 wt% of a preservative. Examples of preservatives used in ophthalmic solutions include benzalkonium chloride, cetrimonium, sodium perborate, sodium chlorite, stabilized oxychloro complex, SofZia,

polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[043] The presence of trace amounts of heavy metals in the buffer solution may accelerate the hydrolysis of muscarinic acetylcholine receptor antagonists which contain a hydrolysable bond. The composition may optionally further comprise a heavy metal chelator, such as the heavy metal chelator ethylenediaminetetraacetic acid (EDTA). The amount of the chelator, e.g., EDTA present in the composition may be from about 10 ppm to 5000 ppm, preferably from about 100 ppm to about 1000 ppm, and more preferably from about 100 ppm to about 500 ppm. In one example the composition comprises 200 ppm or 150 ppm EDTA.

[044] The composition may optionally further comprise an agent capable of increasing intermolecular hydrogen bonding. These agents may help to further stabilize the muscarinic acetylcholine receptor antagonist after autoclave resulting in fewer muscarinic acetylcholine receptor antagonist degradation products. Preferably, the presence of the agent capable of increasing intermolecular hydrogen bonding results in at least 5% (by weight) fewer muscarinic acetylcholine receptor antagonist degradation products than an otherwise identical control composition without the agent capable of increasing intermolecular hydrogen bonding following autoclave. Examples of agents capable of increasing intermolecular hydrogen bonding include trehalose, ethylene glycol, and mannitol. Preferably the agent capable of increasing intermolecular hydrogen bonding is trehalose.

[045] The agent capable of increasing intermolecular hydrogen bonding may be present in the composition in an amount of about 0.1 wt % to about 10.0 wt %. Preferably, the composition comprises from about 0.5 wt % to about 5.0 wt % agent capable of increasing intermolecular hydrogen bonding, more preferably from about 1.0 wt % to about 4.0 wt %, even more preferably

from about 2.0 wt % to about 3.0 wt %. In some examples, the composition may comprise 2.0 wt. % trehalose.

[046] Intermolecular hydrogen bonding can also be increased by formulating the composition with deuterated water (D₂O) instead of regular water. Thus, in some examples, the heat stable ophthalmically-acceptable aqueous liquid composition comprises an amine buffer and a muscarinic acetylcholine receptor antagonist which comprises a hydrolysable bond, wherein the aqueous component of the composition consists of or comprises deuterated water.

[047] The liquid composition has an ophthalmically-acceptable osmolarity. An ophthalmically-acceptable osmolarity is in the range of about 200 mOsm/kg to about 400 mOsm/kg, and typically from about 270 mOsm/kg up to about 330 mOsm/kg.

[048] The liquid composition optionally comprises a tonicity agent in an amount to maintain an ophthalmically-acceptable osmolarity, such as about 0.1 wt.% to 5.0 wt.%, or about 0.5 wt.% to about 3.0 wt.%. Suitable tonicity agents include sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[049] The liquid composition optionally comprises an excipient that extends the period of time that a dose of the composition remains in contact with the cornea. For example, the excipient may be a viscosity-enhancing agent and/or a mucoadhesive agent. Suitable viscosity-enhancing agents include cellulose-based polymers (e.g., hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, and hydroxyethyl cellulose), polyoxyethylene-polyoxypropylene

triblock copolymers (e.g., Poloxamer 407), dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, gellan gum, xanthan gum, guar gum, tamarind seed polysaccharide, hyaluronic acid, or combinations thereof.

[050] In one example, the composition is formulated as a sustained release liquid. For example, the composition may be in the form of an ophthalmic suspension comprising mucoadhesive microspheres which sustain release of the muscarinic acetylcholine receptor antagonist. Methods of making mucoadhesive microspheres for ophthalmic suspensions are described in the literature (see e.g., Dandagi et al., *Sci Pharm* (2013) 81(1):259-280).

[051] The liquid composition may optionally contain additional ingredients such as a comfort agent, a hydrophilic polymer, a wetting agent, a surfactant or other additive.

[052] The invention also provides a container containing a heat-stable ophthalmically-acceptable liquid composition as described herein. In some examples the container is heat-sterilized. In other examples the container is not heat-sterilized, and the ophthalmically-acceptable liquid composition is filter-sterilized. The container may be an eye drop dispenser such as an eye drop dispensing bottle or vial. The dispenser may be single use or multiple use. Some eye drop dispensers have a nozzle connected to a receptacle containing the liquid composition. The receptacle may have deformable walls so that the user can squeeze the receptacle to force the liquid composition into the nozzle. The nozzle allows a drop of the composition to be administered in the lower conjunctival sac and thus to the surface of the eye. Alternatively, a multidose dispenser may comprise a bottle containing the liquid composition of the invention, a tip or dropper, and a closure cap. The bottle may be rigid, for example, made from glass or a rigid plastic. The bottle may have a removable pipette with a deformable bulb to control movement of the liquid within the dropper.

[053] The receptacle can typically hold a volume of 0.01mL to 20 mL. Single use dispensers typically contain sufficient fluid to provide the dosage required by a patient at one time. This may be a single drop for a single eye, or multiple drops (e.g., 2 or 3) for one or both eyes. Single use dispensers typically hold a volume of 0.01 mL to 0.1 mL. Multiple use dispensers contain multiple doses for administration a number of times, and typically hold a volume of 1.0 mL to 20 mL. Preferably, the multiple use dispenser is compatible for use with devices designed to aid the instilling of eye drops.

[054] The container may also contain a contact lens. The container may comprise a base member comprising a bowl that defines a blister cavity dimensioned to accommodate the contact lens and the liquid composition and a flange projecting away from the blister cavity. The base member can be formed from any suitable material, such as glass or a thermoplastic material. A liquid-tight seal can be provided by a cover attached to the flange region, such as a removable foil that is glued or heat sealed to the flange region. Such contact lens containers (i.e., packages), which are commonly referred to as “blister packs”, are well-known in the art (see e.g., U.S. Pat. No. 7,426,993). Generally, the container is configured to receive a single contact lens and an amount of liquid composition sufficient to completely cover the contact lens, typically about 0.5-1.5 mL. The contact lens may be a so-called “myopia control” contact lens having a lens design that slows progression of myopia. Myopia control lenses are well-known in the art (see e.g. U.S. Pat No. 7,832,859, U.S. Pat. No. 8,899,749, and U.S. Pat. No. 11,934,043).

[055] The container can also be a “foil to foil package” which comprises two foil members bonded together, which may either be flat, or one or both foil members formed into an appropriate geometric shape to accommodate contact the lens and liquid composition. In another example, the container is in the form of a plastic base member comprising a plurality of threads and the cover

comprises a plastic cap member comprising a compatible set of threads for engagement with the threads of the base member thereby providing a resealable cover. It will be appreciated that other types of containers can be used.

[056] The sealed package may be sterilized by sterilizing amounts of radiation, including heat or steam, such as by autoclaving. Preferably, the packaged contact lens is sterilized by autoclaving. Autoclaving contact lens packages generally involves subjecting the sealed contact lens package to temperatures of at least 121°C for at least 30 minutes at 17 psi (117 kPa).

[057] The liquid composition of the invention can be used to treat an ophthalmic disorder. Preferably, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. The invention also provides a heat-stable, ophthalmically-acceptable liquid composition for use in medicine. Specifically, the heat-stable, ophthalmically-acceptable liquid composition can be used in the treatment of an eye disorder, such as myopia.

[058] The heat-stable, ophthalmically-acceptable liquid composition is formulated for administration onto the surface of the eye. It is not formulated for administration via injection.

[059] The following Examples illustrate certain aspects and advantages of the present invention, which should be understood not to be limited thereby.

[060] **Example 1: Effect of Buffer on Autoclave-Stability of Atropine**

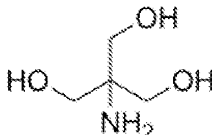
[061] A study was conducted to evaluate the stability of atropine in various buffer solutions after autoclave at pH 6~7. Buffer formulations are provided in Tables 1 to 5. Structures are provided of the amine component of the amine-containing buffers.

[062] TABLE 1: Phosphate Buffered Saline (PBS)

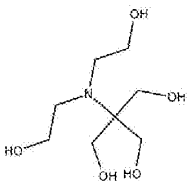
Ingredient	Composition wt%
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Sodium Chloride	0.830%
Sodium Phosphate Monobasic	0.071%
Sodium Phosphate Dibasic	0.599%
Water	98.500%

[063] TABLE 2: EBS Solution

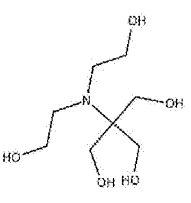
Ingredient	Composition wt%	Amine component
Sodium Chloride	0.920%	
Tris (hydroxymethyl) aminomethane	0.024%	
Tris (hydroxymethyl) aminomethane hydrochloride	0.130%	
Ethylenediaminetetraacetic acid disodium salt dihydrate	0.018%	
Tween 80	0.005%	
Water	98.903%	

[064] TABLE 3: Bis-Tris Solution

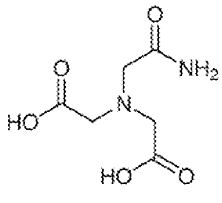
Ingredient	Composition wt%	Amine component
Sodium Chloride	0.894%	
Bis (2-hydroxyethyl) amino- tris(hydroxymethyl)methane	0.050%	
Water	99.056%	

[065] TABLE 4: Bis-Tris Solution with 2% Trehalose (T)

Ingredient	Composition wt%	Amine component
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Sodium Chloride	0.702%	
Bis (2-hydroxyethyl) amino-tris(hydroxymethyl)methane	0.200%	
Trehalose	2.000%	
Water	97.098%	

[066] TABLE 5: ADA Solution

Ingredient	Composition wt%	Amine component
Sodium Chloride	0.816%	
N-(2-Acetamido) iminodiacetic acid	0.190%	
Water	98.994%	

[067] Atropine (dl-atropine, Sigma) was dissolved in each buffer to obtain 0.1% solutions and pH was adjusted to the values shown in Table 7 using HCl or NH₄OH. 4 mL of each solution was added to 6 mL glass vials and sealed with a cap. The vials were autoclaved at 121° C for 30 minutes at 17 psi (117 kPa) (n = 3).

[068] Reverse phase HPLC was used to detect the presence of racemic atropine using the conditions shown in Table 6.

[069] TABLE 6:

Parameter	Reverse phase HPLC
Column	Atlantis T3 5µm 4.6x250mm Part#186003748 with Guard column
Temperature	30°C
Mobile phase	Trifluoroacetic acid in water (0.05% v/v)-acetonitrile (80-20)
Elution rate	1 mL/min
Detector	UV at 256 nm

[070] The percentage of atropine degradation from the autoclaved samples compared to the pre-autoclaved composition is shown in Table 7.

[071] TABLE 7:

Buffer	% decomposition after autoclave at different pH		
	pH 7.0	pH 6.5	pH 6.0
PBS	58.4 %	-	11.8 %
EBS	4.1 %	-	1.2 %
ADA	16.1 %	-	4.2 %
Bis-Tris	11.3 %	2.7 %	1.7 %
Bis-Tris+T	6.5 %	-	0.4 %

[072] **Example 2: Effect of Buffer on Autoclave-Stability of Pirenzepine**

[073] Solutions of 0.1% pirenzepine hydrochloride (Cayman Chemical) were prepared by dissolving pirenzepine into each buffer solution and adjusting pH to the values shown in Table 8 using HCl or NH₄OH.

[074] The solutions were placed in vials and autoclaved as described above for atropine. Analysis was carried out by reverse phase HPLC with UV detector at 281 nm. The percentage of pirenzepine degradation from the autoclaved samples is shown in Table 8.

[075] TABLE 8:

Buffer	% decomposition after autoclave at different pH		
	pH 7.0	pH 6.5	pH 6.0
PBS	8.8 %		2.9 %
EBS	1.4 %		0.8 %
Bis-Tris	2.0 %	0.6 %	0.1 %

[076] The results suggest that pirenzepine is thermally more stable in EBS and Bis-Tris solution than in PBS solution. Amine-type non-phosphate buffers are beneficial in improving the stability of atropine and pirenzepine.

[077] **Example 3: Effect of Citrate Buffer on Autoclave-Stability of Atropine**

[078] A study was conducted to compare the autoclave stability of atropine in citrate, PBS, and Tris-bis buffers at pH 6 to 7. The formulations for the PBS and Bis-Tris buffers are provided above in Tables 1 and 3, respectively. The formulation for the citrate buffer is in Table 9.

[079] TABLE 9: Citrate Buffer

Ingredient	Composition wt%
Sodium Chloride	0.771%
Trisodium Citrate	0.243%
Citric Acid	0.034%
Water	98.952%

[080] Solutions of 0.05% atropine were made in each buffer and pH was adjusted to the values shown in Table 10. Vials of each atropine solution were autoclaved and analyzed by reverse phase HPLC using the methods of Example 1. Results are shown in Table 10 and Figure 1.

[081] TABLE 10:

Buffer	% decomposition after autoclave at different pH			
	pH 5.8-5.9	pH 6.0-6.1	pH 6.3-6.4	pH 6.6-6.7
PBS	6.8 %	13.7 %	17.7 %	-
Citrate	13.5 %	21.3 %	-	43.3%
Bis-Tris	-	0.5%	1.9%	3.7%

[082] The results show that the rate of atropine decomposition is greater in a citrate-based buffer than PBS. The atropine composition comprising an amine buffer is the most stable over a range of pH.

[083] The disclosure herein refers to certain illustrated examples, it is to be understood that these examples are presented by way of example and not by way of limitation. The intent of the foregoing detailed description, although discussing exemplary examples, is to be construed to cover all modifications, alternatives, and equivalents of the examples as may fall within the spirit and scope of the invention as defined by the additional disclosure.

[084] Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

[085] The present invention can include any combination of the various features or embodiments described above and/or in the claims below as set forth in sentences and/or paragraphs. Any combination of disclosed features herein is considered part of the present invention and no limitation is intended with respect to combinable features.

[086] Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It

is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

WHAT IS CLAIMED IS:

1. A heat-stable, ophthalmically-acceptable aqueous liquid composition comprising an amine buffer and a muscarinic acetylcholine receptor antagonist which comprises a hydrolysable bond.
2. The heat-stable, ophthalmically-acceptable liquid composition of claim 1, having a pH in the range of 5.0 to 7.5.
3. The heat-stable, ophthalmically-acceptable aqueous liquid composition of claim 1, having a pH of 5.8 to 7.4.
4. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the hydrolysable bond is an ester bond or an amide bond linked to a nitrogen-containing heterocyclic group.
5. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the muscarinic acetylcholine receptor antagonist is atropine or pirenzepine.
6. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the composition is preservative-free.
7. The-heat stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the composition further comprises EDTA.
8. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the amine buffer is selected from Tris(hydroxymethyl)aminomethane (Tris), N-(2-Acetamido)iminodiacetic acid (ADA), bis(2-Hydroxyethyl)iminotris(hydroxymethyl)methane (Bis-Tris), 2-morpholinoethanesulfonic acid (MES), histidine, ethanolamine, hydrazine, imidazole, pyridine and piperazine.
9. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the amine buffer is selected from Tris and Bis-Tris.

10. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the composition further comprises an agent capable of increasing intermolecular hydrogen bonding.

11. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, comprising an aqueous component that consists of or comprises deuterated water.

12. The heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim, wherein the composition further comprises trehalose.

13. A heat-sterilized container containing the heat-stable, ophthalmically-acceptable aqueous liquid composition of any preceding claim.

14. The heat-sterilized container of claim 13, wherein the liquid composition comprises less than 10% hydrolysed degradation products of the muscarinic acetylcholine receptor antagonist.

15. The heat-sterilized container of claim 13 or 14, wherein the container is a multi-use or single-use eye drop dispensing bottle or vial.

16. The heat-sterilized container of any one of claims 13-15, wherein the container further contains a contact lens.

17. The heat-sterilized container of any one of claims 13-16, wherein the amount of muscarinic acetylcholine receptor antagonist in the composition is no less than 90% of an initial amount of the muscarinic acetylcholine receptor antagonist present in the composition prior to heat-sterilization.

18. The heat-sterilized container of any one of claims 13-17, wherein the composition comprises at least 90% (by weight) fewer hydrolysed degradation products of the muscarinic acetylcholine receptor antagonist than a control composition comprising PBS instead of the amine buffer.

19. The heat-sterilized container of any one of claims 13-18, wherein the heat-sterilized container is sterilized by autoclaving.

20. A method of manufacturing the heat-sterilized container of any one of claims 13-19 comprising:

- (a) placing an ophthalmically-acceptable packaging solution in a container,
- (b) sealing the container, and
- (c) heat sterilizing the sealed container, wherein the packaging solution is the liquid ophthalmically acceptable composition.

21. A container containing the ophthalmically-acceptable aqueous liquid composition of any one of claims 1-12, wherein the liquid composition has been sterilized by filtration.

22. The container of claim 21, wherein the container is a multi-use or single-use eye drop dispensing bottle or vial.